The present Office Action has imposed a second restriction requirement upon Group I, with claims 1-4, and 8-27 remaining in Group I, while claims 28, 29 and 30[1] are restricted into Group V, and claims 50-53 are restricted to Group VI. In response to this second restriction requirement, Applicants elect, with traverse, Group I (Claims 1-4 and 8-27) for examination in the present application.

Accordingly, claims 1-4, 8-30 and 50-53 are pending in the application. Claims 28-30 and 50-53 are provisionally withdrawn from consideration due to Applicants' provisional response to the second restriction requirement

However, Applicants respectfully submit that the second restriction requirement is improper and respectfully request that claims 1-4, 8-30, and 50-53, be examined in the present application.

Applicants note that a proper restriction requirement requires both (1) that the inventions must be independent or distinct as claimed *and* (2) there must be a serious burden on the Examiner (MPEP § 803). Applicants respectfully submit that claims 1-4, 8-30, and 50-53, all involve the use of a recombinagenic oligonucleobase for the introduction of a genetic alteration within a plant cell, or within a plastid of a plant cell. Accordingly, Applicants consider the subject matter of claims 28-30 and 50-53 sufficiently related that of claims 1-4 and 8-27, to support the concurrent examination of all of these claims. Applicants further note that the subject matter of Groups I, V, and VI, has been classified in Class 434, subclass 238, indicating, again, that the recited inventions are closely related to one another. Applicants respectfully submit that the examination of the claims 1-4, 8-30, and 50-53 would not impose an undue burden upon the Examiner since the present Examiner has already done so in the corresponding PCT application (PCT/US98/16267) and found no prior art that even allegedly rendered the invention obvious or not-novel. Accordingly, since the present Restriction Requirement does not meet the standards set forth in MPEP § 803 for a proper restriction, Applicants respectfully request that the present Restriction Requirement be withdrawn and claims 1-4, 8-30, and 50-53 be examined together in the present application.

The claims have been amended in response to the rejection under Section 112, first paragraph. Support for the amendments can be found in the second line of the first paragraph of the Application.

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[1] Claim 30 was not included in any group of the second restriction requirement. Nonetheless, as claim 30 depends from claim 29, Applicants believe that claim 30 was intended to be placed in Group V.

The Rejection of Claims 1-4, and 8-27 Under 35 U.S.C. § 112, First Paragraph, for Lack of Enablement

Claims 1-4, and 8-27 are rejected under 35 U.S.C. § 112, first paragraph, as the Application allegedly does not enable those skilled in the art to practice an invention commensurate in scope with the claims. The Office Action makes three specific allegations in support of the rejection under Section 112, first paragraph.

Firstly, the Office Action at page 4, last sentence, has rejected the claims under Section 112, first paragraph, as follows:

> As not all localized mutation are likely to cause a change in the phenotype of the transgene plant cell, the question is whether a person with skill in the art will be able to identify transgenic cell containing the localized mutation in the absence of any morphological, physiological or biochemical indication.

Each of the non-canceled independent claims, claims 1, 16, 28 and 50, have been amended to required that the localized mutation cause a desired trait. Accordingly, the rejection, which concerns mutations that have no phenotypic effects, is rendered moot by these amendments.

Secondly, the Office Action alleges in the sentence bridging pages 3 and 4 that the Application does not enable one skilled in the art to make localized mutations in non-selectable or non-scorable plant genes, *i.e.,* mutations that do not result in selectable or scorable marker.

Applicants note that the Application provides two methods to be used by those skilled in the art to construct and detect isolates carrying non-selectable and non-scorable localized mutations. In the first, transformation is carried out using a mixture of a mixed duplex oligonucleotide (MDON) or a DNA carrying a selectable marker and a MDON carrying the non-selectable marker of interest (first 4 lines of page 4; paragraph spanning the bottom of page 9 to the top of page 10; and the paragraph spanning the bottom of page 10 to the top of page 11 of the application as filed). Since the expected frequency of co-transformation is in the range of 1% to 10% (page 11, first full paragraph), it would be apparent to one skilled in the art that non-selectable and non-scorable localized mutations could be readily detected within the selected population using methods well known in the art, including but not limited to PCR amplification of a designated target sequence.

Applicants also teach (last sentence of page 26) that the frequency with which a localized, non-selectable mutation is introduced using the materials and methods disclosed in the subject application, using a scorable marker, is 8 in 300,000. A mutation causing a non-selectable or non-scorable trait would be expected to be introduced at the same rate. Applicants, therefore, submit that the frequency of 8 in 300,000 with which a localized, non-selectable mutation can be introduced into a genome is sufficiently high that so that those skilled in this art could isolate a plant having such mutation by the application of routine techniques. As evidence thereof, Applicants provide the accompanying Declaration under 37 C.F.R. § 1.132 of Dr. Keith A. Walker. This Declaration states that it is within the routine practice in the field of plant genetic to screen very large numbers of potential transformants for those isolates carrying the non-selectable or non-scorable marker of interest. In particular, at paragraph 7, the Declaration states that a mutation rate of 8 in 300,000 is sufficient to enable one skilled in the art to isolate a plant having a desired, non-scorable or non-selectable trait caused by the mutation. At paragraph 10 the Declaration further states:

> [B]ased upon my knowledge, experience and familiarity with the present invention and with the scope of efforts routinely used by those skilled in the art, I would respectfully disagree with the assertion that the scope of enablement of Application is limited to scorable or selectable markers. It is my opinion, based upon the information summarized in paragraphs above, that one skilled in the art would be able to practice the invention described in the Application and by use of resources routinely available to those working in the plant development introduce a mutation that causes any desired trait, even a trait that could be detected only by growing and screening a whole plant or plant seed.

Accordingly, Applicants respectfully traverse the allegation that the present specification does not enable one skilled in the art to construct and detect non-selectable or non-scorable localized mutations in a plant gene.

Thirdly, at page 5, first full paragraph, the Office Action alleges that the Applicants have not taught one skilled in the art criteria for selecting the nucleotide sequence making up a recombinagenic oligonucleobase to be used to effect the desired genetic change. Specifically, "Applicants have provided no specific guidance as to how to select the nucleotide sequences which will produce a protein or polypeptide conferring the desired trait."

Applicants respectfully traverse. At the outset, Applicants note that their invention is a general method for introducing predetermined localized genetic alterations in plant cells. Each person who practices the invention will do so in the context of a unique research and development program in plant science. Enablement of a general method of introducing pre-determined alterations in plant cells does not require that the applicants conceive and describe all of the desired alterations that can be introduced using the method. The specific desired traits and the means of obtaining such traits are not a part of the Applicants' generic invention. Therefore the invention is enabled even without a teaching as to each such alteration that may prove desirable.

However, Applicants have also provided numerous examples of mutations to be introduced into plant gene that will result in both selectable and non-selectable properties. Section 4.6, entitled "Specific Genes That Can Be Transmutated to Create Selectable Traits" provides examples of specific, selectable mutations that are introduced into plant genes encoding: acetolactate synthase, the D1 subunit of photosystem II of the chloroplast, dihydropicolinate synthase, threonine dehydratase and the S14/rp59 ribosomal protein. In addition, in Section 4.7 of the present application, entitled "Genes That Can Be Mutated to Create Desirable Non-Selectable Traits," Applicants have disclosed many examples of target genes and appropriate mutations or classes of mutations, to be introduced into plant cells to effect desired phenotypes related to male sterility, carbohydrate metabolism of tubers, post-harvest browning of plant products, lignin reduction in wood pulp, reduction in unsaturated and polyunsaturated lipids in oil seeds, inactivation of genetic mechanisms preventing self-fertilization to allow the development of inbred lines of such plants, and ethylene insensitivity to obviate over-ripening of fruit.

In summary, Applicants respectfully submit that each of the bases for the rejection under Section 112, first paragraph, has been obviated or overcome in light of: (1) the present Amendments to the claims reciting that the localized mutation of the invention cause a desired trait; (2) the attached Declaration of Dr. Walker, demonstrating that the invention introduces a localized mutation at a rate which is sufficient to allow those skilled in the art to isolate a plant having such a mutation causing a non-selectable or non-scorable trait; and (3) the teaching of the Application of numerous examples of genes that can be advantageously mutated by the present invention and the legal principle that the invention of a generic method is sufficiently enabled without a specific teaching as to all the potential uses of the method.

Accordingly, Applicants respectfully request that the rejection of claims 1-4 and 8-27 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

CONCLUSION

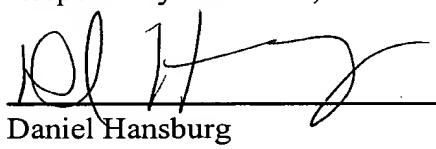
Applicants submit that claim 1-4, 8-30, and 50-53 are in condition for allowance, early notice of which is earnestly requested.

Should the Examiner determine not to grant the Applicants' request, then a personal or telephonic interview is requested to discussion ways of addressing the Examiner's remaining concerns. The undersigned can be reached at 212 790 6550.

If it would be appropriate and helpful, Dr. Walker could be made available for a personal interview to address and respond to any concerns the Examiner may have.

Respectfully submitted,

Date December 29, 1999



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Daniel Hansburg (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Enclosure